What is the therapeutic value of antidepressants in dementia? A narrative review

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WHAT IS THE THERAPEUTIC VALUE OF ANTIDEPRESSANTS IN DEMENTIA? A NARRATIVE REVIEW

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Key points:

- There is little evidence of the therapeutic value of using antidepressants in dementia whatever the indication
- A better understanding of the aetiologies underlying neuropsychiatric symptoms in dementia would assist the development of future treatments
- Antidepressants have adverse effects when used in those with dementia
- Further large scale high quality RCTs are needed to test the role of antidepressants in under-researched areas such as anxiety and agitation in dementia and discontinuation of antidepressants in dementia

ABSTRACT

Objectives: Antidepressants are commonly used in dementia. Depression is a frequent and important co-morbidity in dementia and antidepressants are often used to treat depression and more widely. However there are questions about their utility in depression in dementia and other behavioural and psychological symptoms of dementia (BPSD). The aim of this narrative review is to summarise the evidence on whether there is therapeutic value in prescribing antidepressants to people with dementia.

Methods: A PubMed search was performed to identify RCTs that prescribed antidepressants to people with dementia, either in the treatment of BPSD (depression, anxiety, agitation/aggression, psychosis, apathy) or for secondary outcomes (quality of life, carer burden, activities of daily living, cognition, clinical severity, adverse events).

Results: Thirty-six RCTs were identified (participant n=3,386). A consistent finding in well-designed blinded placebo controlled trials in dementia is the lack of positive effect of antidepressants on outcomes of interest including depression. One large well-designed study has reported a significant reduction in agitation in people with dementia, but at the expense of clinically significant adverse events. Otherwise change observed in open trials is also seen in the placebo group, suggesting any effect is not attributable to the prescription of antidepressants.

Conclusions: It is striking how few data there are on indications other than depression. We should question the use of antidepressants in dementia. Definitive trials of clinical effectiveness of specific indications such as anxiety and agitation in dementia and discontinuation of antidepressants in dementia are needed.

INTRODUCTION

Antidepressants are commonly used in dementia, but do they do any good? Depression is a frequent and important co-morbidity in dementia and antidepressants are often used to treat the syndrome of depression. They are also used to treat other behavioural and psychological symptoms of dementia (BPSD) (Finkel *et al*., 2000) including agitation, aggression, psychosis and apathy (Burns and Iliffe, 2009). There is a need for effective treatment of depression and other BPSD, because of their profound negative impact on individuals with dementia and their caregivers. They complicate patient care (Bharucha *et al*., 2002), increase the cost of care (Beeri *et al*., 2002) and result in caregiver burden (Coen *et al*., 1997), rapid cognitive decline (Stern *et al*., 1987), impairment in activities of daily living (ADL) (Lyketsos *et al*., 1997; Mok *et al*., 2004) and poorer quality of life (QoL) (González-Salvador *et al*., 2000). Each of these has a profound negative impact on both the person with dementia and carers, so treatment is a clinical priority.

Systematic reviews of the literature have generally found little or equivocal evidence for the effectiveness of antidepressants in the treatment of depression in dementia (Bains *et al*., 2002; Nelson and Devanand, 2011) or BPSD (Sink *et al*., 2005). Despite this, 25-42% of all those with dementia may be prescribed antidepressants (Pitkala *et al*., 2004; Snowdon *et al*., 2011). Due to their widespread use in the absence of definitive evidence of their effects and side effects in populations with dementia, it is important to establish their efficacy and tolerability in dementia. No review to date has taken account of the multiple potential targets for antidepressants in dementia. In this narrative review we seek to present RCT data to enable a balanced appraisal of the use of antidepressants in dementia across indications.

REVIEW

This paper is a narrative review. In comparison to a systematic review, a narrative review is less formal and systematic and subjective methods are used to interpret information, which is then summarised subjectively and narratively (Klassen *et al*., 1998). We chose this format rather than that of a systematic review because of the nature of the data available and the breadth of the question posed. Formal systematic review methodology is not well suited to answering multiple questions in a broad literature of variable quality.

We performed a literature search using the PubMed database for peer-reviewed publications available on 9 December 2015, without language restrictions. The following search terms were used; 'depression', 'dementia', 'Alzheimer's disease', 'antidepressant', 'SSRIs', 'anxiety', 'agitation', 'aggression', 'psychosis', 'apathy', 'behavioural and psychological symptoms', 'BPSD' and 'CSDD' (Cornell Scale for Depression in Dementia). Results were filtered to include only RCTs. For inclusion, RCTs were required to have an antidepressant treatment arm being administered to a dementia population. Trials were excluded if the sample population were cognitively healthy or had mild cognitive impairment (MCI). In trials with both dementia and non-dementia participants, outcomes for the dementia subgroup needed to be reported separately. There was no exclusion criteria based on age, gender or dementia subtype. Trials were excluded if they did not use validated measures of the following outcomes: depression, agitation/aggression, anxiety, apathy, psychosis, cognitive status, functional status, carer burden, QoL, clinical severity and global BPSD. Systematic reviews and meta-analyses were sought

through PubMed and The Cochrane Library to provide guidance on the narrative and to identify additional studies that may have been missed in the initial search. Titles and abstracts were independently screened by two authors (NF and LM) before full-texts were obtained and screened.

Following exclusions, the search identified thirty-four RCTs; two additional RCTs were identified after reading relevant literature (Finkel *et al.*, 2004; Gaber *et al*., 2001). A summary of outcome measures of identified RCTs were extracted (Table 1). Information on sample population, intervention type and results associated with antidepressant treatment and how they compared to a placebo group or comparator, were also extracted (Table 2). All data were extracted by a single author (NF) and independently verified by a second author (LM). In addition to the RCTs, we identified three Cochrane reviews (Bains *et al.*, 2002; Martinón-Torres *et al.,* 2004; Seitz *et al.,* 2011) and six systematic reviews (Henry *et al*., 2011; Leong, 2014; Nelson and Devanand, 2011; Sepehry *et al*., 2012; Sink *et al*., 2005; Thompson *et al*., 2007).

Risk of bias was subsequently assessed using The Cochrane Collaboration's tool for assessing risk of bias (Higgins *et al.,* 2011) by NF and independently confirmed by SB. The tool was used as means to describe the risk of bias and it was not used a means to exclude any studies. The majority of studies were deemed as having 'unclear' or 'low' risk of bias across all elements. Many of the unclear judgements were as a result of poor reporting. For example, the majority of studies reported as "double-blind" did not describe the steps they took to ensure this and whether it was successfully maintained. Nine studies were deemed to have at least 1 element of

high risk of bias. One study (Moretti *et al.,* 2002) had multiple elements judged as having a high risk of bias; this was largely due to the fact it was not double-blinded. Three studies were judged to have low risk of bias across all elements: HTA-SADD (Banerjee *et al.,* 2013, 2011), DIADS-II (Drye *et al.,* 2011; Martin *et al.,* 2006; Rosenberg *et al.,* 2010; Weintraub *et al.,* 2010), and CitAD (Peters *et al.,* 2015; Porsteinsson *et al.,* 2014) (Table 3).

Antidepressants for depression in dementia

Apart from a few exceptions (e.g. Choe *et al*., 2015; Pollock *et al*., 2002), it is clear that most individuals recruited into trials of selective serotonin reuptake inhibitor (SSRI) antidepressants or serotonin-noradrenaline reuptake inhibitors (SNRIs) have experienced reduced depressive symptoms from baseline to endpoint (Banerjee *et al*., 2011; Bergh *et al*., 2012; Karlsson *et al*., 2000; Katona *et al*., 1998; Lyketsos *et al*., 2003, 2000b; Magai *et al*., 2000; Moretti *et al*., 2002; Mowla *et al*., 2007; Nyth *et al*., 1992; Nyth and Gottfries, 1990; Petracca *et al*., 2001; Taragano *et al*., 1997; Nyth and Gottfries, 1990). However, the same magnitude of change is seen in the placebo group so these decreases in depression are not attributable to the antidepressants. Two trials found a significant improvement above that of placebo (Lebert *et al*., 2004; Lyketsos *et al*., 2003); they were both small in sample size and Lebert and colleagues did not use a measure of depression validated in dementia (Lebert *et al*., 2004).

The quality of the studies available is an important consideration. The Cochrane review *Antidepressants for treating depression in dementia* (Bains *et al*., 2002) identified only four studies which reported sufficiently detailed results to enter into a

meta-analysis, with a total of 137 subjects. The review concluded that the evidence for clinical effectiveness of antidepressants for depression in dementia was equivocal and weak and that the small possibility of positive effect was driven by the highly positive DIADS study of sertraline (Lyketsos *et al*., 2003). Since that review, the much larger DIADS-II study (Drye *et al*., 2011; Rosenberg *et al*., 2010; Weintraub *et al*., 2010) has yielded robust data demonstrating that sertraline is not superior to placebo in the treatment of depression in dementia. They found no benefit of sertraline over placebo at 12 or 24 weeks. When these data are added to those from the HTA-SADD Trial (Banerjee *et al*., 2013, 2011), which found no superiority of sertraline over placebo in a larger sample (n=326) at 13 and 39 weeks of treatment, the evidence base suggests that SSRI antidepressants do not appear to work as a treatment for depression in dementia.

There are a number of older and generally smaller trials which have investigated tricyclic antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) (Petracca *et al*., 1996; Reifler *et al*., 1989; Roth *et al*., 1996; Teri *et al*., 1991). The quality of these studies reflects their age; the outcome measures used are not developed or validated for use in dementia; these studies often do not meet the quality thresholds needed for inclusion in modern systematic reviews. Two RCTs explored the effects of imipramine on depression in dementia and found no benefit over placebo (Teri *et al*., 1991; Reifler *et al*., 1989). In a very small double-blind cross-over RCT of clomipramine, participants receiving the treatment significantly improved in Hamilton Depression Rating Scale (HDRS) score and remission rate, compared to placebo (Petracca *et al*., 1996). Similarly, Roth and colleagues found the MAOI, moclobemide had some effect in improving HDRS scores in a mixed

group of cognitive impairment in comparison to placebo (Roth *et al*., 1996). Quality issues in the design of these studies as well as the appreciable side effects of these classes of antidepressants, mean that their clinical utility remains unproven.

Few trials have investigated the effects of newer, non-SSRI antidepressants on depression in dementia. The HTA-SADD trial, found that treatment with mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), was no better than treatment with placebo over 13 and 39 weeks (Banerjee *et al*., 2013, 2011). Fuchs and colleagues reported that the tetracyclic antidepressant maprotiline was significantly better at improving depression scores compared to placebo on the Geriatric Depression Scale (GDS; p=0.09) (Fuchs *et al*., 1993). Caution should be taken interpreting this on methodological grounds; statistical significance was set at 10% rather than the usual 5% level and the GDS has limitations in populations with dementia (Burke *et al*., 1989; Kørner *et al*., 2006).

A balanced appraisal of the evidence suggests, taking into account the methodological limitation of older studies, that the antidepressants tested to date show no convincing advantage over placebo for the treatment of depression in dementia.

Antidepressants for anxiety in dementia

Despite anxiety being common in dementia (Badrakalimuthu and Tarbuck, 2012) and previous recommendations to use antidepressants in its treatment (Sink *et al*., 2005), few RCTs have investigated the effects of antidepressants on anxiety in dementia. In four trials, treatment had no significant effect on anxiety score over placebo (Lebert

et al., 2004; Teranishi *et al*., 2013; Nyth *et al*., 1992; Nyth and Gottfries, 1990). In all four trials anxiety was only measured using subscale of a broader assessment tool. One other RCT used a specific and validated measure of anxiety (Petracca *et al*., 2001) but again found no significant improvement in anxiety scores compared with placebo.

What is striking is the lack of large well-designed trials designed to generate a definitive appraisal of the clinical effectiveness of antidepressants for anxiety in dementia. Despite its reported impact on those with dementia and their carers, the management of anxiety in dementia has attracted little attention in terms of research and/or funding. This area would benefit from further research.

Antidepressants for agitation in dementia

Agitation, defined as inappropriate verbal, vocal or motor activity, which is not an expression of unmet need, and which encompasses physical and verbal aggression (Cohen-Mansfield and Billig, 1986), is particularly problematic in dementia. It can affect 50% of people with AD over a month (Okura *et al*., 2010) and appears to persist (Ryu *et al*., 2005). It is associated with deteriorating relationships with family and professional carers, institutionalisation, increased costs of care, carer burden, carer burnout and decreased QoL (Okura *et al*., 2010; Ryu *et al*., 2005; Wetzels *et al*., 2010). As such, it is a legitimate target for intervention (Banerjee, 2009). Antipsychotic medication, the current mainstay of drug treatment for agitation and aggression in dementia, has only a limited positive effect in treating symptoms and can cause significant harm to people with dementia (Banerjee, 2009; Gill *et al*., 2007).

Despite much research, no other drugs have a proven positive role in the treatment of agitation, but antidepressants have been considered as a possible alternative to antipsychotics (Tariot *et al*., 1998, 1995). Sulzter and colleagues compared the efficacy of trazodone to haloperidol, in the treatment of agitation in dementia (Sultzer *et al*., 2001, 1997). Results indicated that they were equally effective overall. Similar findings have been reported comparing sertraline to haloperidol treatment (Gaber *et al.*, 2001). However, the small sample sizes (n=28 and 23 respectively) and lack of a placebo group in both trials, limit the interpretation of these findings. They are not likely to have been powered appropriately to make valid inferences of equivalence of effect.

Two studies have reported that antidepressants reduce agitation compared to placebo in dementia (Pollock *et al*., 2002; Porsteinsson *et al*., 2014), however much of the literature has found no significant treatment effect (Auchus and Bissey-Black, 1997; Finkel *et al*., 2004; Lanctôt *et al*., 2002; Magai *et al*., 2000; Pollock *et al*., 2007; Sultzer *et al*., 2001, 1997; Teranishi *et al*., 2013; Teri *et al*., 2000). One potential limitation of the majority of these studies (all but Auchus and Bissey-Black, 1997; Porsteinsson *et al*., 2014; Sultzer *et al*., 2001, 1997), is that they treated agitation as a continuous variable and did not require participants to have clinically significant agitation on enrolment.

The best trial in this area is the large (n=186) well-designed CitAD trial (Peters *et al*., 2015; Porsteinsson *et al*., 2014). In this 9 week RCT comparing citalopram with placebo, all participants had probable AD and clinically significant agitation. The trial

found that citalopram led to a reduction in agitation, measured by the agitation subscale of the Neurobehavioral Rating Scale (−0.93 (95% CI, −1.80 to −0.06), p=0.04). CitAD provides evidence that 30mg citalopram daily has a positive effect on agitation in dementia. It also confirms safety concerns for citalopram (US FDA, 2012). The adverse cardiac effects identified in the trial, and to a lesser extent the cognitive impairment observed, is likely to limit use in clinical practice (National Institute for Health and Care Excellence, 2014). The CitAD trial is however encouraging, this evidence of antidepressant efficacy supports the need for further research and is a proof of the concept that antidepressants as a class of drugs may have a role in the management of agitation in dementia.

Antidepressants for psychosis in dementia

Psychotic symptoms (hallucinations and delusions) may affect 60% of those with dementia (Ballard *et al*., 1995). Antipsychotic medication is traditionally used to treat psychotic symptoms in dementia, in line with treatment practice in those without cognitive impairment. However, as noted above antipsychotics are associated adverse events in dementia including an increase in mortality (Gill *et al*., 2007; Schneider *et al*., 2005). In light of this, there is a desire to test alternate treatments such as antidepressants. In a recent RCT (Teranishi *et al*., 2013), 82 patients with dementia and neuropsychiatric symptoms were randomly assigned to receive risperidone, fluvoxamine or yokukansa (a traditional Japanese herbal remedy) for 8 weeks. Those receiving fluvoxamine had a significant improvement in delusion but not hallucination scores over the trial, but there were no between-group effects on either delusion or hallucination scores and no placebo with which to compare the effects.

Other trials have reported similar findings (Bergh *et al*., 2012; Lebert *et al*., 2004; Pollock *et al*., 2007, 2002; Sultzer *et al*., 2001) but these are largely secondary analyses of RCTs designed to investigate other primary hypotheses. So participants were generally not selected on the basis of having psychosis in dementia, the measures chosen often lack in detail and the trials do not include a placebo group (all but Pollock *et al*., 2002). An exception is the small study by Levkovitz and colleagues where 20 participants with AD and psychotic symptoms were randomly assigned perphenazine with either fluvoxamine or placebo in a 6 week cross-over RCT (Levkovitz *et al*., 2001). Those receiving adjunctive fluvoxamine significantly improved scores on the Brief Psychiatric Rating Scale (BPRS) compared to placebo.

At present, the evidence base for the value of antidepressant use for psychosis in dementia is weak with little suggestion of positive effect. There would be value in further research in this area.

Antidepressants for apathy in dementia

Apathy is a core element of depression and so separating it from depression is problematic. However, there have been observations of apathy without apparent depression in dementia, so apathy has been proposed as a behavioural syndrome characterized by a decrease in interest, motivation, or initiation of action (van Reekum *et al*., 2005). Apathy so defined is a common neuropsychiatric syndrome in AD, with a prevalence of 92% in severe AD (Mega *et al*., 1996). There is little evidence to support the notion that antidepressants might have a specific effect on apathy in dementia. Bergh and colleagues discontinued SSRI medication for 25

weeks in 63 patients with AD, VaD or mixed dementia with neuropsychiatric symptoms (Bergh *et al*., 2012). Apathy scores were found not to differ significantly between those that discontinued or continued SSRI treatment. Fluvoxamine (Teranishi *et al*., 2013), trazodone (Lebert *et al*., 2004), and citalopram (Pollock *et al*., 2002) have also been reported to have no effect on apathy scores.

No trial to date has defined participants by clinical level of apathy at baseline. There is little evidence for a role of antidepressants in the specific treatment of apathy in dementia.

Antidepressants and carer burden in dementia

BPSD is associated with carer burden (Burns and Rabins, 2000; Coen *et al*., 1997). Few trials have explored the impact of antidepressants given to the person with dementia on carer burden; in most no significant treatment effects were observed (Auchus and Bissey-Black, 1997; Banerjee *et al*., 2013, 2011; Finkel *et al*., 2004; Lyketsos *et al*., 2003; Teri *et al*., 2000). Two studies reported that antidepressants had a positive effect on carer burden (Moretti *et al*., 2002; Porsteinsson *et al*., 2014) both also showed the antidepressant improved BPSD, suggesting a pathway to relief of carer burden via the relief of BPSD in the person with dementia. In terms of objective burden, HTA-SADD found those randomised to mirtazapine required half the unpaid carer time, compared with those receiving placebo or sertraline (Romeo *et al*., 2013). It is possible this effect was mediated via the putative ability of mirtazapine to ameliorate sleep disturbance. Improvements in sleep could potentially release carer time directly and address an important source of carer distress. In this

way an antidepressant might have a general effect, beneficial for both the patient and the carer, without exerting a specific antidepressant effect.

Antidepressants and activities of daily living in dementia

Function in terms of ADL is a common secondary outcome measure when investigating the effects of antidepressants in dementia. All but two studies suggest that antidepressants do not further impair ADL in dementia (Banerjee et al., 2013, 2011; Bergh et al., 2012; Finkel et al., 2004; Lyketsos et al., 2003, 2000a; Moretti et al., 2002; Petracca et al., 1996, 2001; Porsteinsson et al., 2014; Reifler et al., 1989; Teranishi et al., 2013; Weintraub et al., 2010). One reported a positive effect (Mowla *et al*., 2007) and one a negative effect (Teri *et al*., 2000). On balance there is no evidence at present to suggest that antidepressants have a positive or negative effect on ADLs in dementia.

Antidepressants and cognition in dementia

In terms of improving cognition in people with dementia, there is little evidence to suggest that antidepressants have any effect. The DIADS, DIADS-II, and HTA-SADD trials of depression in dementia, all showed no effect on cognition in those randomised to sertraline or mirtazapine treatments compared with placebo treatment (Banerjee *et al.,* 2013, 2011, Lyketsos *et al.,* 2003, 2000a; Munro et al., 2004; Rosenberg *et al.,* 2010). This has been echoed in other studies investigating the effects of other antidepressants (Choe *et al*., 2015; Levkovitz *et al*., 2001; Olafsson *et al*., 1992; Teri *et al*., 1991; Weintraub *et al*., 2010). There is some evidence to suggest that cognitive function (Petracca *et al*., 1996; Porsteinsson *et al*., 2014; Teri *et al*., 2000) or specific cognitive measures (Deakin *et al*., 2004; Reifler *et al*., 1989)

may be negatively impacted by some antidepressants. However, a few trials also exist which have reported a significant improvement in cognitive performance following treatment compared to placebo (Mowla *et al*., 2007; Nyth *et al*., 1992; Roth *et al*., 1996). It is important to note however, that bar a few exceptions (e.g. Deakin *et al*., 2004; Mowla *et al*., 2007; Munro *et al*., 2012, 2004; Olafsson *et al*., 1992; Teri *et al*., 1991), most RCTs do not use a comprehensive cognitive battery. Instead many RCTs have explored cognition using a single global cognitive measure; typically the Mini Mental State Examination (MMSE). Cognition is a secondary outcome in these studies and the MMSE is used to primarily to describe the sample rather than as a discriminative outcome measure.

Adverse events of antidepressants in dementia

Whilst the effects of antidepressants on BPSD and other secondary outcomes in dementia are equivocal at best, it is clear that antidepressants cause a set of adverse events. Commonly occurring adverse events include: anxiety and nervousness (Auchus and Bissey-Black, 1997; Finkel *et al*., 2004), tremors (Auchus and Bissey-Black, 1997; Lanctôt *et al*., 2002), anorexia (Finkel *et al*., 2004; Moretti *et al*., 2002; Porsteinsson *et al*., 2014; Teranishi *et al*., 2013) and falls (Lanctôt *et al*., 2002; Teranishi *et al*., 2013). In addition, the level of adverse event reporting is high in absolute terms. HTA-SADD reported 43% of participants receiving sertraline and 41% receiving mirtazapine showed adverse reactions compared to 26% on placebo (Banerjee *et al*., 2011). Porsteinsson and colleagues found 96% of participants taking citalopram had an adverse event (Porsteinsson *et al*., 2014), with diarrhoea, anorexia, fever, impaired cognition and QT interval prolongation significantly greater in the citalopram group compared to placebo. Despite the levels of adverse events

being high, study discontinuation appears relatively low and not higher in those receiving antidepressant treatment compared to placebo (9.0% vs 6.0% respectively) (Nelson and Devanand, 2011).

DISCUSSION

The findings from this narrative review of the literature suggest that despite being very commonly used, the evidence for antidepressants having a positive role in dementia is weak. A consistent finding is that any change observed in outcomes is also seen in the placebo group. There is no good evidence that antidepressants are effective in improving depression, ADL, cognition or carer burden. There are however harms that are attributable to the use of antidepressants, which are common and in some cases serious (Drye *et al*., 2014; Porsteinsson *et al*., 2014). In view of these adverse effects, the lack of evidence for positive effects, and how commonly they are prescribed, further trials investigating the effect of withdrawing antidepressants in dementia from those where they have been used for long periods would be of value.

To be clinically useful, studies need well defined and relevant sample populations. From this review it is apparent that many past trials have explored the effects of antidepressants on a large battery of secondary outcomes, in trials designed to test other hypotheses. However, there has been a positive move to greater methodological precision in recent trials of antidepressants in dementia (Banerjee *et al*., 2011; Porsteinsson *et al*., 2014; Rosenberg *et al*., 2010). This includes larger sample sizes with greater power, more generalisable study populations, correct use of blinding and placebo groups, greater specificity in the population chosen for study

(e.g. depression in dementia, agitation in dementia) and clarity in the primary outcomes, secondary outcomes and the measures chosen to assess them. The data from such trials are much more likely to be of direct clinical relevance and to generate definitive results.

It is important to note that there are several limitations of this review. First, whilst every attempt was made to identify the relevant literature by having broad search terms and searching citations, there is the possibility that some trials may have been missed. Second, this review did not exclude any study on the basis of their study quality, this may lead the significance of some findings to be over reported. We have attempted to account for this by putting a greater emphasis on larger studies, which have been judged to have a lower risk of bias.

The lack of efficacy in treating BPSD with antidepressants is perhaps understandable when we consider that we are trying to treat a complex phenomenon with a simple intervention. Antidepressants that work in cognitively normal groups of older people with depression do not seem to work in those with depression in dementia. In part, this is likely to be due to greater heterogeneity in depression in dementia compared to depression without dementia. Dementia introduces multiple extra dimensions of complexity. Depression in dementia is likely to include at least three distinct groups:

(i) A group where depression is situationally determined as a reaction to the impacts of dementia and may respond to problem solving and support. This is akin to ‘reactive’ depression and might respond to clinical support provided by

dementia diagnostic and care services rather than to antidepressants. This would explain some of the positive change observed in those receiving placebo (but also usual care) in studies including DIADS-II and HTA-SADD.

(ii) A homophenotypic group where the syndrome looks like depression but may have a different biological basis that is a function of the neurodegeneration of the dementia process. This group is likely to have a different neurochemistry compared with depression in those without dementia. This might explain the different (poorer) response to antidepressant treatment in those with depression in dementia.

(iii) A group who carry a past history of depression (given it is a recurrent disorder) into dementia or who develop a 'true' episode of major depressive disorder in dementia. In these cases antidepressant response may be similar to that in depression without dementia, but there might also be attenuation in treatment response due to the neurodegeneration and neurochemical changes that are part of dementia.

There are data to support such heterogeneity. Zarb reported cognitively impaired patients with higher verbal intellectual functioning were more likely to be depressed (Zarb, 1996). This might be due to greater embarrassment and sadness at their memory decline or a greater awareness of their impairment. Conversely, denial of memory deficits has been found to be negatively associated with depression (Sevush and Leve, 1993). People with depression in dementia have neuropathological differences compared to patients without depression including

degeneration of the locus coeruleus and substantia nigra (Zubenko and Moossy, 1988) or the locus coeruleus and the central superior nucleus (Zweig *et al*., 1988). Degeneration of these nuclei are associated with deficits in noradrenaline and serotonin, both of which are related to mood (Zubenko *et al*., 1990; Zweig *et al*., 1988).

Research that seeks to develop treatments for AD and other dementias is increasingly aware of the complexity of these disorders, of the multiple aetiologies that may lead to these syndromes, and which may determine differential treatment response. These findings underline that this complexity is just as likely to be active in the BPSD that drive QoL in dementia, as in dementia itself. Current clinical practice in the use of antidepressants in dementia is more based in an altruistic desire to do something positive about BPSD whilst trying to avoid the harms that come from other drugs like antipsychotics, than it is based upon evidence.

We need better treatments for BPSD. There are intriguing signals in the literature (such as the halving of carer time seen with mirtazapine in HTA-SADD and the positive effects on agitation in CitAD) that antidepressants may have a valuable role in their management. We need to continue the programme of large good quality placebo-controlled RCTs following up leads from the literature to generate the evidence needed for us to be able to treat BPSD effectively and safely, maximising quality of life for those with dementia and their carers.

LIST OF ABBREVIATIONS

AChEIs: Acetylcholinesterase inhibitors; AD: Alzheimer's disease; ADL: activities of daily living; ADRQL: Alzheimer's Disease Related Quality of Life; BPSD: Behavioural and Psychological Symptoms of Dementia; BPRS: Brief Psychiatric Rating Scale; CSDD: Cornell Scale for Depression in Dementia; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision); GDS: Geriatric Depression Scale; HDRS: Hamilton Depression Rating Scale; MAOIs: Monoamine Oxidase Inhibitors; MMSE: Mini Mental State Examination; NBRS-A: Neurobehavioral Rating Scale agitation subscale; NPI: Neuropsychiatric Inventory; RCTs: randomised controlled trials; QoL: quality of life; RSS: Relative Stress Scale; SSRI: selective serotonin reuptake inhibitor; TCAs: tricyclic antidepressants; VaD: Vascular dementia.

COMPETING INTERESTS

SB has received consultancy fees, speakers' fees, research funding or educational support to attend conferences from pharmaceutical companies involved in the manufacture of antidepressants, antipsychotics and antidementia drugs, and has been employed by the Department of Health for England. NT and LM declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

NF wrote the first draft of the manuscript, to which SB and LM made substantial contributions. Subsequent drafts were revised by all authors. All authors read and approved the final manuscript. SB acts as guarantor of the work.

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Table 1: A description of outcome measures related to RCTs identified in the review. Measures are not included if outcome data is not reported in relation to time or treatment effects of the antidepressant.

	Outcomes										
AUTHOR	**Aggression/ Agitation**	**Anxiety**	**Apathy**	**Depression**	**Psychosis**	**Cognition**	**Functional**	**Caregiver Burden**	**QoL**	**Global BPSD**	**Clinical Severity**
Auchus and Bissey-Black, 1997	CMAI							CSI		BEHAVE-AD	
Banerjee *et al*., 2013, 2011 (HTA-SADD)				CSDD		MMSE	BADL	SF-12, GHQ-12, ZCBI	DEMQOL, DEMQOL-proxy, self-rated EQ-5D, proxy-rated EQ-5D	NPI	
Bergh *et al*., 2012	NPI*		NPI*	CSDD	NPI*		PSMS		QoL-AD patient, QoL-AD carer	NPI	CDR, SIB
Choe *et al*., 2015				CSDD		ADAS-cog, MMSE				NPI	
de Vasconcelos Cunha *et al*., 2007				MADRS							CGI
Deakin *et al*., 2004						CANTAB				NPI, CBI	
Drye *et al*., 2011; Rosenberg *et al*., 2010; Martin *et al.,* 2006; Weintraub *et al*., 2010 (DIADS-II)				CSDD		MMSE	ADCS-ADL		ADRQL	NPI	mADCS-CGIC

AUTHOR	Outcomes: Aggression/ Agitation	Anxiety	Apathy	Depression	Psychosis	Cognition	Functional	Caregiver Burden	QoL	Global BPSD	Clinical Severity
Finkel *et al*., 2004	CMAI			HDRS		MMSE, ADAS-COG	ADFACS	CBQ		NPI, BEHAVE-AD	CDR, CGI-I, CGI-S
Fuchs *et al*., 1993				GDS		MMSE					
Gaber *et al.,* 2001	CMAI										
Karlsson *et al*., 2000				MADRS							
Katona *et al*., 1998				MADRS, CSDD						GBS	CGI-S, CGI-I
Lanctôt *et al*., 2002	NPI*, BEHAVE-AD*, CMAI									NPI, BEHAVE-AD	
Lebert *et al*., 2004	NPI*	NPI*	NPI*	NPI*	NPI*	MMSE				NPI	CGI-I
Levkovitz *et al*., 2001				HDRS	BPRS						CGI
Lyketsos *et al*., 2000				CSDD, HDRS		MMSE	PDRS-ADL				
Lyketsos *et al*., 2003; Munro *et al*., 2004 (DIADS)				HDRS, CSDD		MMSE, EOWPVT-R, HVLT-R, WISC-R, RBMT: Narrative	PDRS-ADL	NPI caregiver distress		NPI	

	Outcomes										
AUTHOR	**Aggression/ Agitation**	**Anxiety**	**Apathy**	**Depression**	**Psychosis**	**Cognition**	**Functional**	**Caregiver Burden**	**QoL**	**Global BPSD**	**Clinical Severity**
						Recall subscale					
Magai *et al*., 2000	CMAI			CSDD, GS, Facial behaviours							
Moretti *et al*., 2002				HDRS		MMSE, TPC, WFs, WFp	IADL	RSS		NPI	
Mowla *et al*., 2007				HDRS		WMS, MMSE	Lawton and Brody ADL				CGI-2
Munro *et al*., 2012						MMSE, ADAS-Cog, Digit Span Subtest, Letter Fluency, Digit Symbol Modalities Test, Finger Tapping Test					
Nyth and Gottfries, 1990		GBS*		MADRS, GBS*						GBS	CGI
Nyth *et al*., 1992		GBS*		GBS*		GBS*					
Olafsson *et al*., 1992						TMT, Finger-Tapping, Picture recognition, picture recall				GBS	

	Outcomes										
AUTHOR	**Aggression/ Agitation**	**Anxiety**	**Apathy**	**Depression**	**Psychosis**	**Cognition**	**Functional**	**Caregiver Burden**	**QoL**	**Global BPSD**	**Clinical Severity**
Peters *et al*., 2015; Porsteinsson *et al*., 2014 (CitAD)	NPI*, CMAI, NBRS-A					MMSE	ADCS-ADL	NPI caregiver distress		NPI	ADCS-CGIC
Petracca *et al*., 1996				HDRS		MMSE	FIM				
Petracca *et al*., 2001		HAM-A		HDRS		MMSE	FIM				
Pollock *et al*., 2002	NBRS*		NBRS*	NBRS*	NBRS*	MMSE					
Pollock *et al*., 2007	NBRS*				NBRS*						
Reifler *et al*., 1989				HDRS		MMSE, DRS	OARS				
Roth *et al*., 1996				HDRS		MMSE, SCAG					BGP
Sultzer *et al*., 2001, 1997	CMAI, OAS			HDRS	BEHAVE-AD*						CGI
Taragano *et al*., 1997				HDRS		MMSE					

	Outcomes										
AUTHOR	**Aggression/ Agitation**	**Anxiety**	**Apathy**	**Depression**	**Psychosis**	**Cognition**	**Functional**	**Caregiver Burden**	**QoL**	**Global BPSD**	**Clinical Severity**
Teranishi *et al*., 2013	NPI*	NPI*	NPI*	NPI*	NPI*	MMSE	FIM			NPI	
Teri *et al*., 1991						MMSE, DRS, FOME, WMS-AL, WMS-LM					
Teri *et al*., 2000	CMAI, ABID					MMSE	IADL	SCB		RMBPC, BRSD	ADCS-CGIC

*A specific items or subscales extracted.

ABID = Agitated Behaviour in Dementia Scale, AChEIs = Acetyl Cholinesterase Inhibitors, AD = Alzheimer's disease, ADAS-COG = Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADCS-ADL = Alzheimer's Disease Cooperative Study- Activities of Daily Living Inventory, ADCS- GDS = Geriatric Depression Scale, ADFACS = Alzheimer's Disease Functional Assessment and Change Scale, ADRQL = Alzheimer's Disease Related Quality of Life, BADL = Bristol Activities of Daily Living, BEHAVE-AD = Behavior Pathology in Alzheimer's Disease Rating Scale, BGP = Rating Scale for Geriatric Patients, BPRS= Brief Psychotic Rating Scale, BPSD = Behavioural and Psychological Symptoms of Dementia, BRSD = Behavioral Rating Scale for Dementia, CANTAB = Cambridge Neuropsychological Test Automated Battery, CBI = Caregiver Burden Inventory, CBQ = Caregiver Burden Questionnaire, CDR= Clinical Dementia Rating Scale, CGI-2= Clinical Global Impression item 2, CGI-I = Clinical Global Impression – Improvement Scale, CGI-S = Clinical Global Impression – Severity Scale, CGIC= Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, CMAI = Cohen-Mansfield Agitation Inventory, CSDD = Cornell Scale for Depression in Dementia, CSI = Caregiver Stress Inventory, DLB = Dementia with Lewy-Bodies, DRS = The Dementia Rating Scale, EOWPVT-R= Expressive One-Word Picture Vocabulary Test-Revised, FIM = Functional Independence Measure, FOME = Fuld Object Memory Evaluation, GBS = Gottfries Brane Steen Scale, GHQ-12= General Health Questionnaire-12, GS= Gestalt Scale, HAM-A = Hamilton Rating Anxiety Scale, HDRS = Hamilton Depression Rating Scale, HVLT-R= Hopkins Verbal Learning Test-Revised, IADL = Instrumental Activity of Daily Living, mADCS-CGIC = modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, MADRS= Montgomery-Asberg Depression Rating Scale, MDD= Major Depressive Disorder, MMSE = Mini-mental state examination, NBRS = Neurobehavioral Rating Scale, NBRS-A = agitation subscale of the Neurobehavioral Rating Scale, NPI = Neuropsychiatric Inventory, PDRS-ADL = Psychogeriatric Dependency Rating Scale – Activities of Daily Living, PSMS = Lawton and Brody's Physical Self Maintenance Scale, QoL-AD = Quality of Life- Alzheimer's Disease Scale, RBMT = The Rivermead Behavioural Memory Test, RMBPC = Revised Memory and Behaviour Problems Checklist, RSS = Relative Stress Scale, SCAG = Sandoz Clinical Assessment-Geriatric Scale, SCB = Screen for Caregiver Burden, SDAT = Senile Dementia of Alzheimer's Type, SF-12 =

Short Form-12 SIB = Severe Impairment Battery Scale, TPC = Ten Point Clock drawing test, VaD= Vascular Dementia, WFp = Word Fluency Phonological Test, WFs = Word Fluency Semantic Test, WISC-R= Wechsler Intelligence Scale for Children-Revised, WMS-AL = Wechsler Memory Scale-Associate Learning, WMS-LM = Wechsler Memory Scale- Logical Memory, ZCBI = Zarit Carer Burden Inventory.

Table 2: A description of identified RCTs and their results. All results are in relation to the effects of antidepressant treatment on outcome measures relevant to this review. Where possible the effects of the antidepressants are compared to a placebo or comparator group.

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Auchus and Bissey-Black, 1997	15	**Dementia:** Probable or possible AD **BPSD:** Agitation (CMAI ≥ 25)	**Fluoxetine** (20 mg/day) **Haloperidol** (3 mg/day) **Placebo**	6 weeks	No treatment by time effect on CMAI (p=0.82), BEHAVE-AD (p=0.67), or CSI (p=0.67).
Banerjee *et al*., 2011; 2013 (HTA-SADD)	326	**Dementia:** Probable or possible AD **BPSD:** Depression lasting ≥4 weeks (CSDD>8)	**Sertraline** (Target dose 150 mg/day) **Mirtazapine** (Target dose 45 mg/day) **Placebo**	39 weeks	Improvement in CSDD was found in sertraline, mirtazapine and placebo groups between baseline and endpoint (significance not reported). At endpoint no significant difference was reported between placebo and sertraline or mirtazapine (p>0.05): MMSE, BADL, NPI, DEMQOL, DEMQOL-proxy, self-rated EQ5D, proxy-rated EQ5D, ZCBI, GHQ-12, SF-12 PCS, SF-12 MCS.
Bergh *et al*., 2012	128	**Dementia:** AD, VaD or mixed dementia **BPSD:** Presence of neuropsychiatric symptoms (but not depression)	**Treatment Discontinued:** Escitalopram, Citalopram, Sertraline, Paroxetine **Continued Treatment**	25 weeks	Compared to those that discontinued treatment, CSDD was significantly lower (p=0.05) at 25 weeks. No significant difference was reported at 25 weeks between groups on measures of NPI (including psychosis, agitation and apathy clusters), PSMS, patient QoL-AD, carer QoL-AD, CDR or SIB (p>0.05).
Choe *et al*., 2015	74	**Dementia:** Probable AD (CDR 0.5-2) **BPSD:** Free from major depression or other major psychiatric illness.	**Escitalopram** (20 mg/day) **Placebo**	52 weeks	There was a significant time effect for ADAS-Cog, MMSE, NPI but not CSDD. Escitalopram did not have a significant greater effect than the placebo group on any outcome measure (p>0.05).
De Vasconcelos Cunha *et al*., 2007	31	**Dementia:** Mild-Moderate dementia (MMSE 10-24) **BPSD:** Major depression	**Venlafaxine** (mean dose 75 mg/day) **Placebo**	6 weeks	Significant time effect observed in MADRS score (p<0.001). No significant treatment effect in MADRS score or CGI scores.

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Deakin *et al*., 2004	10	**Dementia:** Frontal variant frontotemporal dementia **BPSD:** No criteria	**Paroxetine** (40 mg/day) **Placebo**	9 Weeks	Reversal component of the visual discrimination task (p=0.05), the errors in the paired-associates learning task (p=0.06) and accuracy of the delayed pattern recognition memory (p=0.02) were impaired in the paroxetine group compared to placebo. NPI, CBI and other CANTAB measures did not significantly differ between groups (p>0.05).
Drye *et al*., 2011; Rosenberg *et al*., 2010; Martin *et al.,* 2006; Weintraub *et al*., 2010 (DIADS-II)	131	**Dementia:** Mild to Moderate AD (MMSE 10-26) **BPSD: "**Depression of AD"	**Sertraline** (Target dose 100 mg/day) **Placebo**	24 Weeks	There were no significant differences on measures of mADCS-CGIC and CSDD at 12 weeks between sertraline and placebo groups (p>0.05).There was no treatment effect on mADCS-CGIC and CSDD scores at endpoint (p>0.05). NPI, ADRQL, ADCS-ADL and MMSE change scores did not significantly differ between treatment groups (p>0.05). Sertraline treatment was not superior to placebo at 24 weeks on mADCS-CGIC (p=0.48) or CSDD (p=0.90) in participants with major depression in dementia. No differences in between treatment groups for either outcome in those with minor depression or AD-associated affective disorder.
Finkel *et al*., 2004	144	**Dementia:** Probable or possible AD (MMSE 8-23) **BPSD:** BPSD (NPI > 5, Individual domain severity ≥ 2)	**Sertraline + Donepezil** (50-200 mg/day) **Placebo + Donepezil**	12 weeks	Change scores between baseline and endpoint were not significantly different between treatment groups on NPI, ADAS-COG, BEHAVE-AD, CGI-I, CGI-S, CDR, HDRS, ADFACS, CMAI, CBQ or MMSE (p>0.05).For the CGI-I, a significant treatment by time interaction was reported on the linear mixed model (p=0.007).
Fuchs *et al*., 1993	127	**Dementia:** Primary degenerative dementia of senile onset (>65 years) **BPSD:** Depression	**Maprotiline** (25-75mg/day) **Placebo**	8 weeks	Video ratings of global impression, cognitive impression and depressive impressive were not significantly different between the treatment or placebo group. MMSE scores were not significantly different between treatment groups. GDS score improved significantly more in the maprotiline group in comparison to the placebo group (p = 0.09). Results were reported at the 10% significance level.

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Gaber *et al*., 2001	23	**Dementia:** Probable AD, VaD or mixed dementia **BPSD: "**Agitation and behavioural disturbances"	**Sertraline** (25-50 mg/day) **Haloperidol** (1-2 mg/day)	10 weeks	CMAI scores significantly improved in both the Sertraline and Haloperidol treatment arms ($p<0.05$). No significant differences were reported between the two treatment groups on CMAI scores.
Karlsson *et al*., 2000	336 (50 dementia)	**Dementia:** Dementia (MMSE 16-24) **BPSD:** Major depression of dysthymic disorder (MADRS ≥ 20)	**Citalopram** (20-40 mg/day) **Mianserin** (30-60 mg/day)	12 weeks	MADRS total score on average decreased 12 points from baseline in the dementia sample regardless of treatment, there was no significant treatment effect ($p>0.05$). Those with dementia responded less well to treatment, as measured by MADRS, than those without dementia ($p<0.04$).
Katona *et al*., 1998	198	**Dementia:** Dementia (MMSE 17-23) **BPSD:** Depression (MADRS ≥ 20)	**Paroxetine** (Target dose 40 mg/day) **Imipramine** (Target dose 100 mg/day)	8 weeks	At endpoint, MADRS improved in both the paroxetine (M=12.6) and imipramine (M=11.8) groups; there was no significant difference between the two treatment groups at any time point ($p> 0.05$). CGI-S improved in both paroxetine (M=1.3) and imipramine (M=1.3) groups at endpoint, but there was no treatment effect at any time point ($p>0.05$). CGI-I improved at endpoint in both paroxetine (M=2.7) and imipramine (M=2.7) groups, though there were no treatment effects at any time point ($p>0.05$). CSDD improved at endpoint in both paroxetine (M=8.9) and imipramine (M=7.1) groups; there was a significant difference between treatment groups at week 4 and 8 ($p<0.05$), but not at endpoint ($p = 0.10$). GBS improved at endpoint in both paroxetine (M=11.7) and imipramine (M=12.0), though there was no significant difference between the two groups at any time point ($p>0.05$).
Lanctôt *et al*., 2002	22	**Dementia:** Probable AD (1 year duration, MMSE < 24) **BPSD:** Significant behavioural problems (NPI ≥ 8)	**Sertraline** (100 mg/day) **Placebo**	4 weeks	There was no significant treatment effect on total NPI or CMAI at the end point of the study ($p>0.05$). No significant differences were reported between sertraline and placebo treatment on CMAI, NPI aggression subscale or BEHAVE-AD aggression subscale change scores ($p>0.05$).

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Lebert *et al*., 2004	26	**Dementia:** FTD (FBDS > 3) **BPSD:** Total score NPI > 8 and one NPI item score of ≥ 4	**Trazodone** (Target dose 300mg/day) **Placebo**	12 weeks (cross over at week 6)	Significant decrease in NPI total score after trazodone treatment compared to placebo ($p<0.05$) however a significant period ($p<0.05$) and sequence effect ($p < 0.05$) was observed. Further analysis revealed that there was a treatment effect of select subscales of the NPI including depression ($p=0.02$) and agitation ($p=0.04$). No significant treatment effect was reported on MMSE, CGI-I, or any other relevant NPI subscale ($p>0.05$).
Levkovitz *et al*., 2001	20	**Dementia:** AD **BPSD:** Psychotic symptoms (BPRS ≥ 18) lasting less than 6 months.	**Fluvoxamine** (50mg/day) **+ Perphenazine** **Placebo + Perphenazine**	6 weeks (crossover at week 3)	Compared to the placebo group, BPRS scores significantly improved in the fluvoxamine group ($p=0.03$).There was also a significant positive effect of fluvoxamine on paranoid ($p=0.03$) and negative ($p=0.02$) symptoms items of the BPRS. There was no significant difference between groups on HDRS, CGI and BPRS ($p>0.05$).
Lyketsos *et al*., 2000	22	**Dementia:** Probable AD (MMSE>10) **BPSD:** Major depressive episode	**Sertraline** (Target dose 150 mg/day) **Placebo**	12 weeks	CSDD significantly improved in the sertraline group at weeks 3, 6, 9, and 12 ($p<0.05$). The sertraline treatment was significantly better at improving CSDD compared to placebo ($p=0.03$). HDRS significantly improved in the sertraline group at weeks 3, 6, 9 and 12 ($p<0.05$). PDRS-ADL scores worsened in placebo group at weeks 9 and 12 ($p<0.05$). There were no significant between group differences in HDRS, PDRS-ADL and MMSE measures.
Lyketsos *et al*., 2003; Munro *et al*., 2004 (DIADS)	44	**Dementia:** Probable AD **BPSD:** Major depressive episodes	**Sertraline** (Mean dose 95 mg/day) **Placebo**	12 weeks	Depression symptoms improved in the sertraline treatment group. Both CSDD ($p=0.002$) and HDRS ($p=0.01$) significantly differed between treatment groups in favour of the sertraline treatment. There were no treatment effects on measures of NPI total, NPI caregiver distress, PDRS-ADL and MMSE ($p>0.05$). There was no treatment effect on the slope of decline over time on any cognitive measure (EOWPVT-R, HVLT-R, WISC-R, RBMT).
Magai *et al*., 2000	31	**Dementia:** Probable or possible AD **BPSD:** Minor and Major depression	**Sertraline** (Target dose 100 mg) **Placebo**	8 weeks	CSDD ($p<0.0001$) and GS ($p<0.05$) improved over time. There were no treatment by time interactions for CSDD, GS, CMAI, and sad face ($p>0.05$). The authors noted that the treatment by time interaction approached significance on the knit-brow face measure in favour of sertraline ($p<0.10$)

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Moretti *et al*., 2002	50	**Dementia:** Probable AD (MMSE ≥ 12) **BPSD:** Not required	**AChEIs + Citalopram** (Target dose 20 mg/day) **AChEIs**	48 weeks	MMSE significantly declined from baseline in both treatment groups (p<0.05), however TPC, WFs, WFp and IADL scores remained unchanged (p>0.05). RSS, NPI and HDRS scores significantly improved between baseline and endpoint (p<0.01). Only RSS, NPI and HDRS scores were significantly lower in citalopram + AChEI group compared to AChEI only group at endpoint (p<0.01).
Mowla *et al*., 2007	122	**Dementia** Alzheimer type (MMSE 10-24) **BPSD:** Not required	**Rivastigmine + Fluoxetine** (20 mg/day) **Rivastigmine** **Placebo**	12 weeks	Those receiving fluoxetine reported a significant improvement in MMSE (p<0.001), WMS (p=0.007), ADL (p<0.001), HDRS (p<0.001) from baseline to endpoint. The MMSE (p=0.002), WMS (p<0.001) and ADL (p=0.001) change scores were all significantly improved in the fluoxetine group compared to the placebo group. CGI-2 scores were significantly better in the fluoxetine group compared to the placebo group (p<0.01).
Munro *et al*., 2012	131	**Dementia:** AD (MMSE 10-26) **BPSD:** "Depression of AD"	**Sertraline** (Target dose 100 mg/day) **Placebo**	24 Weeks	There was no significant difference between sertraline and placebo group on any cognitive test performance at endpoint (p>0.05).
Nyth and Gottfries, 1990	98	**Dementia:** SDAT, AD or VaD **BPSD:** Not required	**Citalopram** (Target dose 30 mg/day) **Placebo**	4 weeks double blind 8 weeks open trial 4 weeks double blind	MADRS score significantly declined between baseline and week 4 (p<0.05), however there was no between group differences on MADRS improvement. CGI scores worsened in the placebo group (p<0.05) but remained unchanged in the citalopram group. Anxiety and depressed mood items of the GBS significantly improved in the citalopram group (p<0.05). Only depressed mood items of the GBS were significantly more improved in the citalopram group compared to placebo group (p<0.05).
Nyth *et al*.,1992	149	**Dementia:** Mild-Moderate dementia **BPSD:** Clinical depression (DSM III; Total HDRS ≥ 14)	**Citalopram** (Target dose 30mg/day) **Placebo**	6 weeks	In GBS items there was a significant improvement from baseline to endpoint in anxiety (p<0.01), depressed mood (p<0.001), orientation in time (p<0.05), personal orientation (p<0.05), recent memory (p<0.01) and distant memory (p<0.05). None of these measures significantly improved in the placebo group between time points. A significant between group difference in improvement scores were reported for orientation in time and recent memory (p<0.05), and trending toward significance in depressed mood (p<0.06).

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Olafsson *et al*., 1992	46	**Dementia:** Primary degenerative dementia or multi-infarct **BPSD:** Not required	**Fluvoxamine** (150mg/day) **Placebo**	6 weeks	No significant time or treatment effects on any of the neuropsychological test scores, GBS scale scores or GBS subscale scores were observed.
Peters *et al*., 2015; Porsteinsson *et al*., 2014 (CitAD)	186	**Dementia:** Probable AD (MMSE 5-28) **BPSD:** Clinically significant agitation	**Psychosocial intervention + Citalopram** (Target dose 30mg/day) **Psychosocial intervention + placebo**	9 Weeks	The citalopram group showed significant improvement compared with placebo in the estimated difference in week 9 scores of NBRS-A (p=0.04) and ADCS-CGIC (p=0.007). Compared to placebo, citalopram was associated with improved scores on the CMAI (p=0.008), NPI total (p=0.01), NPI agitation (p =0.12) and NPI caregiver distress (p=0.02). A significant negative effect was reported in those receiving citalopram compared to placebo for MMSE scores (p=0.03). There was no significant difference between groups on the ADCS-ADL scale (p=0.32).
Petracca *et al*., 1996	24	**Dementia:** Probable AD **BPSD:** HDRS > 10	**Clomipramine** (Target dose 100mg/day) **Placebo**	14 weeks (cross over after 6 weeks RCT and a 2 week wash-out)	Significant time effect on HDRS scores ($p < 0.001$) but participants taking clomipramine showed greater improvement during the first 6-week treatment period ($p < 0.01$). Remission (HDRS ≤ 7) numbers were greater for participants started on clomipramine compared to those that started on placebo ($p = 0.02$). Significantly lower MMSE scores in the clomipramine group compared to placebo ($p < 0.01$). No significant treatment effects on FIM scores.
Petracca *et al*., 2001	41	**Dementia:** Probable AD **BPSD:** Major or minor depression	**Fluoxetine** (Target dose 40 mg/day) **Placebo**	6 Weeks	HDRS scores improved in both groups over time ($p<0.001$), however, there was no significant group effect or group by time interaction ($p>0.05$). HAM-A scores improved in both groups over time ($p<0.001$), however there was no significant group or group by time interaction ($p>0.05$).FIM scores improved in both groups over time ($p<0.001$) however there was no significant group effect of group by time effect. MMSE scores showed no significant time, group or group by time interaction ($p>0.05$).

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Pollock *et al*., 2002	85	**Dementia:** AD, VaD, mixed type, or dementia otherwise not specified **BPSD:** One target symptom (NBRS ≥ 3) in agitation items or psychosis items	**Citalopram** (Target dose 20 mg/day) **Perphenazine** (Mean dose 6.5 mg/day) **Placebo**	17 days	Only depression and apathy NBRS subscale scores did not significantly improve from baseline in the citalopram group (p>0.05). Cognition, agitation, and psychosis significantly all improved from baseline to endpoint (p<0.05). A significant difference between citalopram and placebo group were only reported in improvements in agitation and liability scores (p<0.05).
Pollock *et al*., 2007	103	**Dementia:** AD, VaD, DLB, mixed, or dementia otherwise not specified **BPSD:** One target symptom (NBRS ≥ 3) in agitation items or psychosis items	**Citalopram** (Mean maximum dose 31.1 mg/day) **Risperidone** (Mean maximum dose 1.36 mg/day)	12 weeks	There was a significant decline in both NBRS agitation (p=0.05) and psychosis (p<0.004) scores in the citalopram treatment group. No significant difference was reported between treatment groups on either measure of agitation of psychosis (p>0.05).
Reifler *et al*., 1989	61 (28 dementia with depression, 33 not depressed)	**Dementia:** AD (MMSE ≤ 25) **BPSD:** Depression (HDRS ≥ 15)	**Imipramine** (mean daily dose 83 mg/day) **Placebo**	6 weeks	Those receiving imipramine showed no significant improvement in HDRS, MMSE and OARS scores compared to placebo (p>0.05). DRS scores declined more significantly in the placebo group compared to patients receiving placebo (p<0.01).
Roth *et al*., 1996	694 (511 dementia with depressive symptoms, 183 depression with cognitive decline)	**Dementia:** Dementia or cognitive impairment (MMSE 11-28) **BPSD:** Depression of Major Depressive Episode (GDS ≥ 5; HDRS ≥ 14 on first 17 items)	**Maclobemide** (400 mg/day) **Placebo**	6 weeks	Significantly greater mean improvements were seen in the moclobemide group compared with placebo on the HDRS (p=0.001), the cognitive disturbance items on SCAG (p=0.05) and MMSE (p=0.05) at 6 weeks. Improvement in total SCAG score and BGP in the maclobemide group did not significantly differ to placebo (p>0.05).

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Sultzer *et al*., 1997; 2001	28	**Dementia:** Dementia **BPSD:** Agitated behaviours (CMAI ≥ 41 or individual item score ≥ 6)	**Trazodone** (mean dose 218 mg/day) **Haloperidol** (mean dose 2.5 mg/day)	9 weeks	There was a significant time effect on CMAI ($p<0.001$), OAS ($p=0.005$) and CGI scores ($p<0.001$), but no significant treatment or treatment by time effect ($p>0.05$). Also, HDRS ($p=0.005$) and the delusion subscale of the BEHAVE-AD ($p=0.01$) improved over time in the trazodone group. However, there was no significant treatment effect at any time point on these measures ($p>0.05$).
Taragano *et al*., 1997	37	**Dementia:** Probable AD **BPSD:** Major Depressive Syndrome	**Fluoxetine** (10 mg/day) **Amitriptyline** (25 mg/day)	6 Weeks	HDRS improved from baseline to endpoint (M=25.3 vs M=16.7) in the in both groups (snr). There was no significant difference between the fluoxetine group compared to the amitriptyline group in terms of the number of participants that reported a >30% reduction on the HDRS or in the improvement in MMSE from baseline to endpoint (M=20.0 vs M=21.4; snr).
Teranishi *et al*., 2013	82	**Dementia:** AD, VaD and DLB (MMSE < 19) **BPSD:** One neuropsychiatric symptom (NPI> 4)	**Fluvoxamine** (25-200 mg/day) **Risperidone** (0.5-2.0 mg/ day) **Yukukansan** (2.5-7.5 g/day)	8 Weeks	NPI scores significantly improved over time in the fluvoxamine group ($p<0.001$). In all three treatment groups, only the delusion ($p=0.012$) and agitation ($p<0.001$) subscales of the NPI were significantly reduced at end point. No significant between group differences were reported on any NPI subscale ($p>0.05$). MMSE and FIM did not change significantly from baseline in the fluvoxamine group ($p>0.05$).
Teri *et al*., 1991	61 (28 with MDD, 33 without)	**Dementia:** Primary Degenerative Dementia (MMSE ≤ 25) **BPSD:** MDD	**Imipramine** (mean dose 82 mg/day) **Placebo**	8 Weeks	There were no significant time by group effects on measures of MMSE, DRS, WMS-AL, WMS-LM or FOME ($p>0.05$).

AUTHOR (TRIAL NAME)	NO. OF PARTICIPANTS	TYPE OF PARTICIPANTS	TREATMENT CONDITIONS	DURATION	RESULTS
Teri *et al*., 2000	149	**Dementia:** Probable or possible AD **BPSD:** 2 week or more history of agitated behaviours occurring at least once weekly	**Trazodone** (Mean dose 200 mg/day) **Haloperidol** (Mean dose 1.8 mg/day) **Behavioural management techniques** **Placebo**	16 weeks	ADCS-CGIC outcomes did not significantly differ between placebo and trazodone groups at endpoint (p=0.99). MMSE change scores were significantly worse in the trazodone group compared to the BMT group (p<0.05). IADL change scores were worse in the trazodone group compared to placebo (p<0.05). ABID, CMAI, BRSD, RMBPC and SCB change scores in the trazodone group did not significantly differ to any other treatment group.

ABID = Agitated Behaviour in Dementia Scale, AChEIs = Acetyl Cholinesterase Inhibitors, AD = Alzheimer's disease, ADAS-COG = Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADCS-ADL = Alzheimer's Disease Cooperative Study- Activities of Daily Living Inventory, ADCS- GDS = Geriatric Depression Scale, ADFACS = Alzheimer's Disease Functional Assessment and Change Scale, ADRQL = Alzheimer's Disease Related Quality of Life, BADL = Bristol Activities of Daily Living, BEHAVE-AD = Behavior Pathology in Alzheimer's Disease Rating Scale, BGP = Rating Scale for Geriatric Patients, BPRS= Brief Psychotic Rating Scale, BPSD = Behavioural and Psychological Symptoms of Dementia, BRSD = Behavioral Rating Scale for Dementia, CANTAB = Cambridge Neuropsychological Test Automated Battery, CBI = Caregiver Burden Inventory, CBQ = Caregiver Burden Questionnaire, CDR= Clinical Dementia Rating Scale, CGI-2= Clinical Global Impression item 2, CGI-I = Clinical Global Impression – Improvement Scale, CGI-S = Clinical Global Impression – Severity Scale, CGIC= Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, CMAI = Cohen-Mansfield Agitation Inventory, CSDD = Cornell Scale for Depression in Dementia, CSI = Caregiver Stress Inventory, DLB = Dementia with Lewy-Bodies, DRS = The Dementia Rating Scale, EOWPVT-R= Expressive One-Word Picture Vocabulary Test-Revised, FIM = Functional Independence Measure, FOME = Fuld Object Memory Evaluation, GBS = Gottfries Brane Steen Scale, GHQ-12= General Health Questionnaire-12, GS= Gestalt Scale, HAM-A = Hamilton Rating Anxiety Scale, HDRS = Hamilton Depression Rating Scale, HVLT-R= Hopkins Verbal Learning Test-Revised, IADL = Instrumental Activity of Daily Living, mADCS-CGIC = modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, MADRS= Montgomery-Asberg Depression Rating Scale, MDD= Major Depressive Disorder, MMSE = Mini-mental state examination, NBRS = Neurobehavioral Rating Scale, NBRS-A = agitation subscale of the Neurobehavioral Rating Scale, NPI = Neuropsychiatric Inventory, PDRS-ADL = Psychogeriatric Dependency Rating Scale – Activities of Daily Living, PSMS = Lawton and Brody's Physical Self Maintenance Scale, QoL-AD = Quality of Life- Alzheimer's Disease Scale, RBMT = The Rivermead Behavioural Memory Test, RMBPC = Revised Memory and Behaviour Problems Checklist, RSS = Relative Stress Scale, SCAG = Sandoz Clinical Assessment-Geriatric Scale, SCB = Screen for Caregiver Burden, SDAT = Senile Dementia of Alzheimer's Type, SF-12 = Short Form-12 SIB = Severe Impairment Battery Scale, TPC = Ten Point Clock drawing test, VaD= Vascular Dementia, WFp = Word Fluency Phonological Test, WFs = Word Fluency Semantic Test, WISC-R= Wechsler Intelligence Scale for Children-Revised, WMS-AL = Wechsler Memory Scale-Associate Learning, WMS-LM = Wechsler Memory Scale- Logical Memory, ZCBI = Zarit Carer Burden Inventory.

Table 3: A summary table of risk of bias assessments for each study.

AUTHOR	Randomisation	Allocation	Blinding of participant and personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other sources of bias
Auchus and Bissey-Black, 1997	?	?	?	?	+	+	+
Banerjee *et al*., 2011; 2013 (HTA-SADD)	+	+	+	+	+	+	+
Bergh *et al*., 2012	+	+	+	+	-	+	?
Choe *et al*., 2015	+	?	+	+	+	?	+
De Vasconcelos Cunha *et al*., 2007	?	?	?	?	-	+	+
Deakin *et al*., 2004	?	?	?	?	+	-	+
Drye *et al*., 2011; Rosenberg *et al*., 2010; Martin *et al.,* 2006; Weintraub *et al*., 2010 (DIADS-II)	+	+	+	+	+	+	+
Finkel *et al*., 2004	?	?	?	?	+	+	?
Fuchs *et al*., 1993	?	?	?	?	+	+	+
Gaber *et al*., 2001	?	?	?	?	?	-	?
Karlsson *et al*., 2000	?	?	?	?	+	+	+
Katona *et al*., 1998	?	?	?	?	+	+	+
Lanctôt *et al*., 2002	?	?	?	?	+	+	+
Lebert *et al*., 2004	?	?	?	?	?	+	+
Levkovitz *et al*., 2001	?	?	?	?	+	-	+
Lyketsos *et al*., 2000	?	?	?	?	+	+	+
Lyketsos *et al*., 2003; Munro *et al*., 2004 (DIADS)	+	+	?	?	+	+	+

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Magai *et al*., 2000	?	?	?	+	+	+	+
Moretti *et al*., 2002	-	-	-	-	+	+	+
Mowla *et al*., 2007	+	?	+	+	+	+	+
Munro *et al*., 2012	?	?	+	?	?	-	+
Nyth and Gottfries, 1990	?	?	?	?	?	+	+
Nyth *et al*.,1992	?	?	?	?	+	+	+
Olafsson *et al*., 1992	?	?	?	?	+	+	+
Peters *et al*., 2015; Porsteinsson *et al*., 2014 (CitAD)	+	+	+	+	+	+	+
Petracca *et al*., 1996	?	?	+	?	+	+	+
Petracca *et al*., 2001	?	?	+	?	+	+	+
Pollock *et al*., 2002	?	?	+	?	+	+	+
Pollock *et al*., 2007	?	?	+	+	+	+	+
Reifler *et al*., 1989	?	?	?	?	+	+	+
Roth *et al*., 1996	?	?	?	?	+	+	+
Sultzer *et al*., 1997; 2001	?	?	?	?	?	+	+
Taragano *et al*., 1997	?	?	?	+	-	+	+
Teranishi *et al*., 2013	+	?	-	+	+	+	+
Teri *et al*., 1991	?	?	?	?	?	+	+

Table 3: A summary table of risk of bias assessments for each study.

AUTHOR	Randomisation	Allocation	Blinding of participant and personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other sources of bias
Teri *et al*., 2000	?	?	?	?	+	+	+

+	Low risk of bias	?	Unclear risk of bias	-	High risk of bias